16. (Amended) The method of claim 6, wherein the *hedgehog* polypeptide sequence is an amino acid sequence of a *hedgehog* protein selected from [the group consisting of SEQ ID No:9,] SEQ ID No: 10, SEQ ID No:11, SEQ ID No:12, SEQ ID No:13, SEQ ID No:14, SEQ ID No:15, [and] SEQ ID No:16, SEQ ID No:17, SEQ ID No:18, and SEQ ID No:20.

17. (Amended) The method of claim 6, wherein the *hedgehog* polypeptide sequence is an amino acid sequence of a Sonic *hedgehog* [protein]polypeptide.

REMARKS

Claims 1-21 constitute the pending claims in the present application. Claims 1-17 were elected with traverse. Applicants will cancel non-elected claims upon indication of allowable subject matter. Applicants amend claims 14-16 to correct the correlation between the claimed SEQ ID Nos and the amended sequence listing of August 20, 2000. Applicants add new claims 22-32. Support for the matter for these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note with appreciation the acknowledgement of the priority claim filed September 11, 1998.

2. Applicants acknowledge the Examiner's comments with respect to the restriction requirement. Applicants respectfully maintain the traversal of the restriction requirement, but will cancel non-elected claims upon notice of allowable subject matter.

3-4. Claims 1-17 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, specifically for failing to enable for methods using hedgehog proteins to affect lung

growth. Applicants respectfully traverse this rejection, in so far as it is maintained over the present amendments.

The important role of *hedgehog* signaling has been extensively studied in numerous developmental contexts including neuronal development, chondrogenesis, left-right asymmetry, and spermatogenesis (page 2, lines 7-8). For example, Sonic hedgehog delivered to developing limb buds results in mirror image duplication of digits, and mis-expression of Sonic hedgehog along the developing neural tube influences the fate of neurons differentiating at various dorsal-ventral positions within the neural tube.

The specification and the art at the time of filing provide extensive support for a role for *hedgehog* signaling in lung development. Sonic hedgehog is expressed in the epithelium of the developing lung, and the *hedgehog* receptor *patched* is expressed in the adjacent mesenchyme (Bellusci et al., 1997).

The Examiner maintains that Applicants have provided "no diseases or conditions known to be affected by hedgehog proteins." Applicants respectfully disagree with this assertion. The specification reviews the recent evidence that mutations in *patched* lead to hereditary skin cancer. "The demonstration that nevoid basal-cell carcinoma (NBCC) results from mutations in the human patched gene provided an example of the roles *patched* plays in post-embryonic development." (page 11, lines 6-8). Applicants have extended these findings to the lung, and propose as one embodiment of the invention the inhibition of *hedgehog* signaling as a treatment for hyperplastic or neoplastic conditions (page 15, lines 26-28). More specifically, "inhibitory forms of the subject *ptc*, *hedgehog*, or *fgf-10* therapeutics may be used as part of a treatment program for small lung cancer (SCLC), as well as non-small cell lung cancer (NSCLC), such as adenocarcinoma, lung cell carcinoma and squamus cell carcinoma."

Applicants' assertion that the inhibition of *hedgehog* signaling would constitute a potential treatment for cancers, specifically of the lung, is supported by the work of Fujita et al. (Fujita et al., 1997, enclosed herewith as Exhibit 1). Fujita et al. demonstrated that Sonic hedgehog is expressed in lung squamous carcinoma cell lines, as well as in some adenocarcinoma cell lines. Treatment of such cell lines with Sonic hedgehog resulted in

increased growth and proliferation, while treatment with Sonic hedgehog antibodies inhibits cell growth.

Applicants maintain that both the specification and the art at the time of filing would enable one of skill in the art to use the invention. Specifically, Applicants have provided extensive support for a role for *hedgehog* signaling in lung development, and have provided specific evidence for a method for decreasing growth and proliferation associated with lung cancer by inhibiting *hedgehog* signaling. The Examiner is reminded that in accordance with MPEP 2164.02, "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first parpagraph, does not turn on whether an example is disclosed. An example may be either working or prophetic."

Furthermore, Applicants submit the following post-filing evidence in the form of a declaration from the inventor. This data, as presented in Exhibits A-E, demonstrates that antagonism of hedgehog signaling promotes lung maturation and surfactant production. A) in situ hybridization data showing that the expression of the downstream mediator of hedgehog signaling, *gli-1*, is down regulated during later lung development. B) depicts the inverse relationship between the expression of *gli-1* and the lung maturation marker, Sp-C. C) shows that treatment of embryonic lung cultures with *hedgehog* antagonist XX decreases *hedgehog* signaling as demonstrated by a substantial decrease in *gli-1* expression. D) shows that *hedgehog* antagonist XX increases the expression of the maturation marker Sp-C. The level of induction of Sp-C in embryonic lung cultures treated with the hedgehog antagonist is similar to that observed following treatment with steroids which are known to increase lung maturation and surfactant production. E) shows the converse experiments where treatment of embryonic lung cultures with a *hedgehog* agonist decreases surfactant production. These experiments identify the inhibition of *hedgehog* signaling as a therapeutic for neonatal respiratory distress syndrome (RDS).

Applicants contend that both the specification at the time of filing and the post-filing evidence provide enablement for the full scope of the claims. Inhibition of hedgehog signaling has a demonstrated influence on lung maturation, as well as tumor progression. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

5-6. Claims 1-17 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. To expedite prosecution, Applicants have amended the claims to incorporate the Examiner's suggestions. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection is requested.

(a) Applicants amendments to claim 1 deleting the term 'ectopic' obviate this rejection.

(b) Applicants traverse the objection to the word 'encodable' in claim 15. Applicants maintain that the term encodable is not indefinite because one of skill in the art would understand the metes and bounds of the claimed subject matter. Applicants also point out that encodable and encoded are not necessarily synonymous terms. These two terms must be evaluated in light of the degeneracy of the genetic code. "Encodable" permits the inclusion of recombinant or variant nucleic acid sequences that are able to encode a given amino acid sequence, and one of skill in the art can readily envision all such sequences based on common knowledge in the art. Accordingly, Applicants submit that use of the word encodable clearly defines the scope of the claimed subject matter, and the Examiner's argument does not indicate otherwise.

Applicants maintain that criteria for stringent hybridization conditions are found on page 22 of the specification, however Applicants have amended claims 15 to more explicitly define the metes and bounds of the stringency conditions.

(c) Applicants have amended the claims to more explicitly define the term 'growth state'. Applicants have amended claims 1 and 2, and added new claims 22 and 23 to more explicitly point out that the claimed therapeutics are agonists or antagonists.

(d) Applicants have amended claim 6 to provide a functional criterion to access the bioactivity of the *hedgehog* polypeptide fragments.

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CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this Reply, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

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Respectfully Submitted,

Date: September 7, 2001

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